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DR. ARLIE R. BARNES, Rochester, *Editor*

DR. T. J. DRY, Rochester, *Associate Editor*

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ANTICOAGULANT THERAPY

Currently there are two preparations; namely, heparin and dicumarol, that are being used clinically for the purpose of preventing thrombosis. Neither preparation possesses the qualities of the ideal anticoagulant. Both preparations require careful and daily observation of the patient who receives them, and neither preparation is practical for long-continued administration. However, sufficient clinical information has now accumulated to show that both preparations are effective in preventing thrombosis and that, when the preparations are used properly, the risk of bleeding is very small. There is no evidence that either preparation has any effect on a thrombus that already has formed.

Heparin. Heparin is prepared commercially from beef lung and dispensed usually in ampules containing 100 mg. in 10 c.c. of solution. It appears to have no toxic effects or significant physiologic effects other than its anticoagulant action. Heparin impairs coagulability of the blood, apparently by inhibiting both the conversion of prothrombin to thrombin and the coagulation of fibrinogen by thrombin. It is only effective when administered parenterally.

Two methods of intravenous administration have been used for the purpose of preventing thrombosis. (1) 100 to 200 mg. (preferably the latter) are added to 1,000 c.c. of a diluent, either a 0.9 per cent solution of sodium chloride or a 5 per cent solution of dextrose. The resulting dilute solution is administered continuously, starting with 25 drops per minute. The number of drops delivered each minute is varied so that the coagulation time of venous blood in a glass tube is kept between fifteen and twenty-five minutes. This necessitates testing the coagulation time every three to six hours during the first twenty-four hours of administration and at least every twelve hours thereafter, because of the variability of sensitivity to heparin in different cases and possibly from time to time in the same case. (2) Repeated intravenous injections of the concentrated solution (10 mg. of heparin per cubic centimeter) are given at the rate of either 5 c.c. (50 mg. of heparin) every four hours or 10 c.c. (100 mg. of heparin) every six hours. This method disregards differences in sensitivity to heparin, and the coagulation time is not determined. In spite of the fact that the coagulation time returns to normal for varying periods between injections, the method seems to be effective.

Heparin can be given intramuscularly in a slowly absorbed medium. Less heparin is used when this technic is followed, but the effect is difficult to control and pain and bleeding may occur at the site of injection.

When given intravenously, heparin acts rapidly and its effect terminates within a few hours after its administration is stopped. However, heparin is expensive and its administration is time consuming and impractical for periods longer than two weeks.

Dicumarol. Dicumarol [3,3'-methylenebis (4-hydroxycoumarin)], originally isolated from spoiled sweet clover, is now made synthetically and usually is dispensed in capsules, each containing 100 mg. It impairs coagulability of the blood by producing prothrombin deficiency as indicated by increase of prothrombin time. The coagulation time of whole blood also may be altered but not proportionately to changes in the prothrombin time. Determination of the coagulation time is not a reliable guide to the action of dicumarol. Dicumarol also may prolong clot retraction and increase the sedimentation rate of the erythrocytes. There is also some evidence that it inhibits adhesiveness of the thrombocytes. Other than these actions, dicumarol appears to have no effect on the human body.

Dicumarol is effective when administered orally. A satisfactory preparation for parenteral use has not been developed. Patients vary greatly in their sensitiveness to dicumarol; therefore, when it is administered a daily test of the prothrombin time is essential in order to be certain that an adequate, but not excessive, effect is being produced. It is advisable that the prothrombin time be expressed as the percentage of the normal prothrombin because thromboplastins used in different clinics and different hospitals in testing the prothrombin time may vary in potency. Also, thromboplastins prepared by the same technic may vary in potency from time to time. It is important that the prothrombin times which correspond to those for 10 per cent, 20 per cent and 30 per cent prothrombin be known each day. To this end, when any particular thromboplastin is used, the prothrombin times for normal plasma and normal plasma diluted to 10 per cent, 20 per cent and 30 per cent with a 0.9 per cent solution of sodium chloride should be checked frequently. When dicumarol is being administered it is advisable that the patient's prothrombin time be kept between the limits indicated by the value for 10 per cent and 30 per cent normal plasma.

The dosage schedule for dicumarol which has been used successfully at the Mayo Clinic for more than five years is as follows: The entire amount for one day is given in a single dose. The first dose is 300 mg. On each subsequent day when the prothrombin is greater than 20 per cent of normal prothrombin, 200 mg. of dicumarol is given. On days when the prothrombin is less than 20 per cent of normal, no dicumarol is given. If the prothrombin drops below 10 per cent of normal during the first few days of treatment and remains there for two days, 20 to 30 mg. of menadione bisulfite is given intravenously, and thereafter only 100 mg. of dicumarol is given to that patient on those days on which the prothrombin is greater than 20 per cent of normal. Using this schedule, prothrombin deficiency has been maintained for as long as six months without untoward or toxic effect on the patient and with return of prothrombin to normal within a few days after administration of dicumarol finally was discontinued.

The disadvantages of dicumarol as an anticoagulant are that its effect is delayed for one or two days (sometimes longer) after administration is begun and that the effect persists for two to seven days after administration is discontinued. It is more diffi-

cult to stop its anticoagulant action than is the case with heparin.

Risk of bleeding. There is some risk of bleeding if either heparin or dicumarol is used. However, this risk is greatly minimized if careful attention is paid to dosage and if an excessive anticoagulant effect is avoided. If bleeding occurs during administration of heparin, it can be stopped rather quickly by discontinuing administration of heparin. If major bleeding occurs during administration of dicumarol, transfusions of fresh citrated blood should be given. These replace lost blood and to some extent supply prothrombin. Also, 60 mg. of menadione bisulfite (synthetic vitamin K) should be given intravenously and the dose repeated once or twice a day until bleeding ceases. The prothrombin deficiency and bleeding usually can be terminated within twenty-four hours by these procedures. Minor bleeding consisting of epistaxis, small hematomas in operative wounds, microscopic hematuria or localized ecchymoses in the skin may occur during administration of dicumarol (in about 3 per cent of cases) but may be disregarded. Major bleeding occurs rarely except from operative wounds or ulceration in the gastro-intestinal tract. In 1,686 cases in which dicumarol was administered postoperatively, such bleeding was encountered in only 1 per cent of the cases in which thrombosis or embolism had occurred prior to the administration of dicumarol and in 2.5 per cent of the cases in which thrombosis or embolism had not occurred.

Contraindications. Obviously, anticoagulant therapy is contraindicated in cases of purpura, in which there is a tendency for the patients to bleed. At the present time, it seems best to consider it contraindicated in subacute bacterial endocarditis because of tendency for spontaneous petechiae and bleeding to occur. There is no good evidence that anticoagulants and penicillin are superior to penicillin alone in the treatment of this disease. Anticoagulants are contraindicated in cases in which an operation recently has been performed on the brain or spinal cord. This is not because the risk of bleeding is greater, but because the consequences of even minor bleeding at the operative site may be great. Dicumarol is contraindicated in cases of renal or hepatic insufficiency because the effect of the drug may be accentuated, greatly prolonged and difficult to control. Dicumarol should be administered cautiously in cases of dietary deficiency although in these cases an excessive response can usually be controlled with synthetic vitamin K. Anticoagulants should be given cautiously to patients who have ulcerative lesions, open wounds and drainage tubes in place, since there is some increased risk of local bleeding in these patients.

Choice of anticoagulants. Because of its low cost and ease of administration, dicumarol has almost entirely supplanted heparin as an anticoagulant in this country. However, when dicumarol is given, preliminary heparinization is advisable in those cases in which a rapid anticoagulant effect is desired. The simplest procedure is to start administration of heparin and dicumarol simultaneously, giving 50 mg. of heparin intravenously every four hours until the prothrombin is less than 20 per cent of normal. Since heparin also affects the prothrombin time, blood for tests of prothrombin time should be withdrawn four hours after a dose of heparin has been given. If anticoagulant therapy is desired and a good setup for determining consistently comparable prothrombin times is not available, only heparin should be used. In cases of hepatic or renal insufficiency also, heparin should be used alone. Heparin is also superior as an anticoagulant for use during and immediately after operations on the blood vessels.

Uses of anticoagulants. The greatest experience with anticoagulants to date has been in the treatment of postoperative thrombo-embolism. In such cases the rationale is predicated on the statistical clinical experience that a patient who has a postoperative pulmonary embolism and survives the first few hours has approximately a 44 per cent chance of having a subsequent thrombo-embolic episode and an 18 per cent chance of having a subsequent fatal embolism. Patients who have a clinically recognizable venous thrombosis or thrombophlebitis have approximately a 25 per cent chance of having a subsequent thrombo-embolic episode and a 6 per cent chance of having a subsequent fatal embolism. When anticoagulant therapy has been used properly in cases of postoperative pulmonary embolism, venous thrombosis and thrombophlebitis, subsequent thrombo-embolic episodes have been almost entirely prevented. In cases in which patients who are to undergo operation have had thrombophlebitis or pulmonary embolism previously, under any circumstances, the risk that postoperative thrombo-embolic complications will develop is increased greatly. The prophylactic use of dicumarol, beginning on the third postoperative day, has been almost entirely effective in preventing such complications. Although rather large numbers of patients who have never had thrombo-embolism have been given prophylactic anticoagulants successfully during the postoperative period, it is not practical at present to use anticoagulant therapy routinely during the postoperative period in all cases. When anticoagulant therapy is used postoperatively, it should be continued for at least ten days and until the patient has been ambulatory for at least three days.

Anticoagulant therapy has also been used successfully in a small series of patients who have had pulmonary embolism, venous thrombosis or thrombophlebitis complicating severe injuries, infectious disease, congestive heart failure and the puerperium. The danger of uterine bleeding in the postpartum period, if anticoagulants are given, is almost nil if there is normal involution of the uterus and if treatment is not begun before the sixth postpartum day.

Anticoagulant therapy is rational, advisable, and has been used successfully as part of the treatment of acute arterial occlusion in the extremities that is due either to arterial embolism or arterial thrombosis in situ. In cases of recurrent idiopathic thrombophlebitis, anticoagulant therapy may be of value during periods when episodes occur frequently but the tendency to recurrence at isolated intervals over long periods limits the effectiveness of such treatment in this disease.

During 1946 there have been three reports of the use of dicumarol immediately after the occurrence of acute coronary occlusion with myocardial infarction. Statistical studies have indicated that the incidence of thrombo-embolic complications is high (approximately 35 per cent), during the six weeks after acute coronary occlusion. Such complications include embolism of the pulmonary, cerebral and peripheral arteries, venous thrombosis and thrombophlebitis. Apparently these thrombo-embolic complications have been reduced to a minimum in a significantly large series of cases in which dicumarol has been administered. There is some evidence that the administration of dicumarol also has inhibited the subsequent development of coronary thrombosis but the continuous use of dicumarol is impractical at present, for a prolonged period during which it might be desirable for this purpose.

Nelson W. Barker, M.D.
Rochester, Minnesota

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